EMA/474721/2019

European Medicines Agency decision

P/0344/2019

of 11 September 2019

on the acceptance of a modification of an agreed paediatric investigation plan for sacubitril / valsartan (Entresto), (EMEA-000316-PIP02-11-M04) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Disclaimer

This decision does not constitute entitlement to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006.

Only the English text is authentic.

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The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0096/2012 issued on 30 May 2012, the decision P/0106/2014 issued on 5 May 2014, the decision P/0240/2015 issued on 30 October 2015, and the decision P/0354/2016 issued on 21 December 2016,

Having regard to the application submitted by Novartis Europharm Ltd. on 17 April 2019 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 26 July 2019, in accordance with Article 22 of Regulation (EC) No 1901/2006,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

(1) The Paediatric Committee of the European Medicines Agency has an opinion on the acceptance of changes to the agreed paediatric investigation plan.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan.

[1] OJ L 378, 27.12.2006, p.1.
[2] OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for sacubitril / valsartan (Entresto), film-coated tablet, age-appropriate solid oral dosage form, oral use, are hereby accepted in the scope set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices.

Article 2

This decision is addressed to Novartis Europharm Ltd., Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

EMA/PDCO/266456/2019
Amsterdam, 26 July 2019

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-000316-PIP02-11-M04

Scope of the application

Active substance(s):

Sacubitril / valsartan

Invented name:

Entresto

Condition(s):

Treatment of heart failure

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Film-coated tablet

Age-appropriate solid oral dosage form

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Novartis Europharm Ltd.

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Novartis Europharm Ltd. submitted to the European Medicines Agency on 17 April 2019 an application for modification of the

agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/0096/2012 issued on 30 May 2012, the decision P/0106/2014 issued on 5 May 2014, the decision P/0240/2015 issued on 30 October 2015, and the decision P/0354/2016 issued on 21 December 2016.

The application for modification proposed changes to the agreed paediatric investigation plan.

The procedure started on 28 May 2019.

Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified.

Opinion

1. The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree to changes to the paediatric investigation plan in the scope set out in the Annex I of this opinion.

   The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the paediatric investigation plan and the subset(s) of the paediatric population and condition(s) covered by the waiver are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the European Medicines Agency, together with its annexes and appendix.

Annex I

The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed Paediatric Investigation Plan

1. Waiver

1.1. Condition

Treatment of heart failure

The waiver applies to:

- the paediatric population from birth to less than 1 month of age;
- for film-coated tablet and for age-appropriate solid oral dosage form, oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric Investigation Plan

2.1. Condition

Treatment of heart failure

2.1.1. Indication(s) targeted by the PIP:

Treatment of heart failure

2.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From one month to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Film-coated tablet

Age-appropriate solid oral dosage form

2.1.4. Studies

Area	Number of studies	Description
Quality	1	**Study 1** Development of an age-appropriate solid oral dosage form.
Non-clinical	3	**Study 2** Mechanistic *in-vitro* study (1170517). **Study 3** 4-week dose range-finding juvenile rabbit bone toxicity study (1170514). **Study 4** 4-week investigative bone study in juvenile rats (1170516).

Clinical	4	**Study 5** Open-label, randomized, single-dose, multiple treatment period study to determine the relative bioavailability of LCZ696 paediatric formulation relative to the LCZ696 200 mg Final Market Image (FMI) tablet in healthy adult subjects (CLCZ696 B2126). **Study 6:** Open-label, multi-centre study to evaluate the safety/tolerability, pharmacokinetics and pharmacodynamics of LCZ696 in paediatric patients from one month to less than 18 years of age with heart failure (CLCZ696B2319 Part 1). **Study 7:** Double-blind, randomized, multi–centre, active controlled, parallel-group study to evaluate the safety and efficacy of LCZ696 vs. enalapril in paediatric patients from one month to less than 18 years of age with symptomatic left ventricular systolic dysfunction and heart failure (CLCZ696B2319 Part 2).

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety or efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By November 2021
Deferral for one or more studies contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of heart failure

Authorised indication(s):

- Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction

Authorised pharmaceutical form(s):

Film-coated tablets

Authorised route(s) of administration:

Oral use